Notice of Allowability	Application No.	Applicant(s)	
	10/542,043	CANTOR ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Amendments of 08/20/2009*.

2. ☒ The allowed claim(s) is/are *1-6 and 8-23*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20091207* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Leena Karttunen on 12/04/2009. During the interview, the Examiner and Applicant's representative discussed and agreed to amendments to the claims consistent with the allowable subject material.

The application has been amended as follows:

The claims of 08/20/2009 have been amended as follows:

Claim 1. A method for determining a haplotype of a subject, the haplotype comprising at least three polymorphic markers that are one or more kilobase pairs apart, comprising the steps of:

(a) diluting a nucleic acid sample from the subject to a single nucleic acid molecule dilution;

(b) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region consisting of about 100 bp, each primer pair thereby producing an amplicon consisting of about 100 bp, and wherein the at least first, second and third primer pair each are designed to amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the first, second, and third nucleic acid region each

comprise at least one polymorphic marker designated as a first, a second and a third polymorphic marker, wherein the first, second and third polymorphic markers are one or more kilobase pairs apart;

(c) genotyping the polymorphic marker in the first, second and third nucleic acid regions using primer extension and MALDI-TOF mass spectrometric detection thereby resulting in a first, a second and a third genotype; and

(d) determining the haplotype comprising polymorphic markers one or more kilobase pairs apart from the first, second and third genotypes to obtain a haplotype for the subject.

Claim 9. A method of diagnosing a disease condition or disease susceptibility by determining a disease related haplotype comprising at least three polymorphic markers that are one or more kilobase pairs apart in a subject, comprising the steps of:

(a) diluting a nucleic acid sample from the subject to a single nucleic acid molecule dilution;

(b) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region consisting of about 100 bp, each primer pair thereby producing an amplicon consisting of about 100 bp, and wherein the at least first, second and third primer pair each are designed to amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the first, second, and third nucleic acid region each comprise at least one polymorphic marker designated as a first, a second and a third

polymorphic marker, wherein the first, the second and the third polymorphic markers are one or more kilobase pairs apart;

(c) genotyping the polymorphic marker in the first, second and third nucleic acid regions using primer extension and MALDI-TOF mass spectrometric detection thereby resulting in at least a first, a second and a third genotype;

(d) determining the haplotype comprising polymorphic markers one or more kilo base pairs apart from the first, second and third genotypes to obtain a haplotype of the subject; and

(e) comparing the haplotype of the subject to known disease-associated haplotypes, wherein a match in the haplotype of the subject with a known disease-associated haplotype indicates that the subject has the disease or that the subject is susceptible for the disease.

Claim 12. A method for determining a haplotype of a subject, the haplotype comprising at least three polymorphic markers that are one or more kilo base pairs apart, comprising the steps of:

(a) treating a nucleic acid sample from the subject with a composition that differentially affects an epigenetically modified nucleotide in the nucleic acid sample to effectively create at least a first, a second and a third polymorphic marker in the nucleic acid sample, wherein each marker is the result of an epigenetically modified nucleotide;

(b) diluting the nucleic acid sample of step (a) to a single nucleic acid molecule dilution;

(c) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region consisting of about 100 bp, each primer pair thereby producing an amplicon consisting of about 100 bp, and wherein the at least first, second and third primer pair each are designed to amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the first, second, and third nucleic acid region each comprise at least one polymorphic marker that is the result of an epigenetically modified nucleotide designated as a first, a second and a third polymorphic marker, wherein the first, the second and the third polymorphic marker are one or more kilobase pairs apart;

(d) genotyping the polymorphic marker in the first, second and third nucleic acid regions using primer extension and MALDI-TOF mass spectrometric detection thereby resulting in at least a first, a second and a third genotype; and

(e) determining the haplotype comprising polymorphic markers one or more kilo base pairs apart from the first, second and third genotypes to obtain a haplotype for the subject.

Claim 17. A method of determining a haplotype in a subject, the haplotype comprising at least three polymorphic markers that are one or more kilobase pairs apart, wherein at least one polymorphic marker is a methylated nucleotide, comprising the steps of:

(a) digesting a nucleic acid sample from the subject with a methylation-sensitive restriction enzyme so that either unmethylated DNA or methylated DNA is left intact, depending on which enzyme is used;

(b) diluting the digested nucleic acid sample of step (a) into a single nucleic acid molecule dilution;

(c) amplifying the single nucleic acid molecule dilution with at least a first, a second and a third primer pair, wherein each primer pair flanks a nucleic acid region consisting of about 100 bp, each primer pair thereby producing an amplicon consisting of about 100 bp, and wherein the at least first, second and third primer pair each are designed to amplify a different nucleic acid region designated as a first, a second and a third nucleic acid region, wherein the first, second, and third nucleic acid region each comprise at least one polymorphic marker, wherein at least one polymorphic marker is a result of a methylated nucleotide, and wherein the at least first, the second and the third polymorphic markers are one or more kilo base pairs apart;

(e) genotyping the polymorphic marker in the first, second and third nucleic acid regions using primer extension and MALDI-TOF mass spectrometric detection thereby resulting in at least a first, a second and a third genotype; and

(f) determining the haplotype comprising polymorphic markers one or more kilo base pairs apart from the first, second and third genotypes to obtain a haplotype for the subject, wherein at least one polymorphic marker next to a methylation site, together with the methylation site, constitutes a haplotype.

Claim 21. The method of claim 1, wherein the at least one polymorphic marker in the first nucleic acid region is three or more kilo base pairs apart from the at least one polymorphic second in the second nucleic acid region.

Claim 22. The method of claim 1, wherein the at least one polymorphic marker in the first nucleic acid region is four or more kilo base pairs apart from the at least one polymorphic marker in the second nucleic acid region.

Claim 23. The method of claim 1, wherein the at least one polymorphic marker in the first nucleic acid region is 15-20 kilo base pairs apart from the at least one polymorphic marker in the second nucleic acid region.

2. The following is an examiner's statement of reasons for allowance:

The objection to claim 7, as set forth on pages 2-3 of the Office Action of 03/05/2009, is **WITHDRAWN** in light of the cancellation of claim 7.

The rejections of claims under 35 USC 103 as obvious in view of the prior art, as set forth on pages 3-18 of the Office Action of 03/05/2009, are **WITHDRAWN** in light of the amendments to the claims which require the amplification of amplicons consisting of about 100 base pairs, and subsequent analysis of the amplicons by MALDI-TOF mass spectrophotometer detection.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHEN KAPUSHOC whose telephone number is (571)272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634